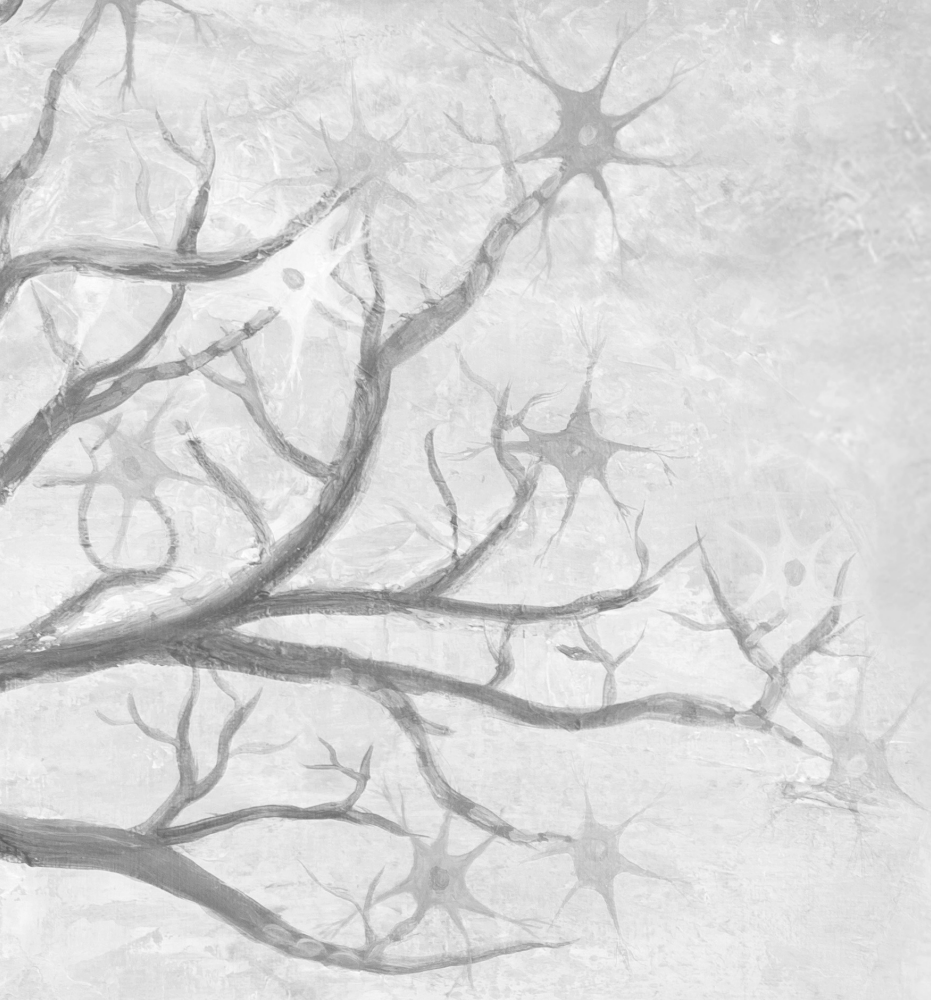

Chapter 2

Quality of general movements in term infants with asphyxia

QUALITY OF GENERAL MOVEMENTS IN TERM INFANTS WITH ASPHYXIA

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Abstract

Background: Perinatal asphyxia may result in a developmental disorder. A recently developed non-invasive tool to investigate brain function at early age is the assessment of general movements (GMs).

Aim: To evaluate relationships between perinatal risk factors and the quality of GMs in the neonatal period and at 3 months in term newborns with asphyxia in a secondary paediatric setting.

Methods: 64 term (>36 weeks postmenstrual age (PMA)) infants with perinatal asphyxia were studied. GMs were assessed at 'writhing' GM age (38 – 47 weeks PMA) and at 'fidgety' GM age (48 – 56 weeks PMA). Pre- and perinatal factors were collected in a standardized way.

Results: Multivariate analysis revealed that DA GMs at 'writhing' age mainly correlated with asphyxia related illness. DA GMs at 'fidgety' age correlated in particular with abnormalities on the neonatal ultrasound scan of the brain.

Conclusion: In secondary paediatric settings GM-assessment especially around 3 months is a valuable tool for the assessment of the integrity of the nervous system in term infants with asphyxia.

Introduction

Perinatal asphyxia is a well known cause of developmental disorders.[1-2] It may result in the development of cerebral palsy (CP), but most cases of CP are not the result of an interruption of oxygen supply around birth.[3-6] In addition, many children born with perinatal asphyxia develop in a typical way.[7-8]

To date it is still unclear which child born with asphyxia will develop neurological impairment and which will not. Recently developed imaging techniques of the newborn brain, such as diffusion weighted MRI and magnetic resonance spectroscopy are promising in this respect,[9-10] but these techniques are not readily available in a secondary paediatric setting. In the more general paediatric setting it remains difficult to predict outcome of perinatal asphyxia. The lack of clinical clarity on prognosis can be explained partially by the variable way in which the term asphyxia is applied. Traditionally the term asphyxia ('being pulseless') was used for infants with a low Apgar score and/or failure to breath.[3,11] Of course a low Apgar score may be the result of perinatal hypoxia or ischaemia, but it may also have been caused by other problems, for example a congenital disorder of the brain.[12] The term asphyxia is also used for conditions in which indirect parameters such as an abnormal fetal heart rate tracing or acidosis suggest the presence of hypoxia and ischemia.[13] Others suggest to use the term asphyxia only for infants born with indicators of hypoxia-ischaemia who present with neonatal encephalopathy.[2.14-15] Here it should be realized however, that - in analogy to CP – a major part of neonatal encephalopathy is not caused by hypoxic-ischaemic insults.[16-17]

The aim of the present study is to analyse the contribution of pre- and perinatal risk factors to the neurological condition at birth and at the age of 3 months in infants with perinatal asphyxia referred to a secondary paediatric department. We included infants with and without neonatal encephalopathy, as this reflects admission practice in the secondary paediatric setting. Neurological condition was assessed by means of the quality of general movements (GMs). The assessment of GMs is a non-

invasive sensitive method to evaluate the integrity of the young nervous system[18-19] and as such complementary to the clinical neurological examination of the paediatrician. A previous study indicated that the assessment of GMs was a good indicator of neurological sequelae in term infants with asphyxia referred to a tertiary care centre.[20] In the latter study all subjects had signs of neonatal encephalopathy as indicated by a Sarnat-score ≥ 2.[21] Other studies evaluated GM-quality in mixed groups of at risk infants, including term infants with perinatal asphyxia. The studies concluded that the assessment of GMs is a valuable and reliable tool to predict later neurological dysfunction and behavioural problems.[22-24]

Subjects and Methods

Subjects

The study group consisted of term infants presenting with perinatal asphyxia admitted to the regional general hospital, Gelre Hospital in Apeldoorn the Netherlands between January 1999 and July 2005. Term birth was defined as birth after 36 completed weeks of gestation. Children were included into the study group, if they fulfilled at least two of the following criteria for asphyxia: 1) abnormal cardiotocogram (CTG), e.g. late decelerations, persistent bradycardia (< 100 beats per minute, or persistent tachycardia (>160 beats per minute)), 2) Apgar score at 5 minutes < 7, 3) umbilical pH < 7.20 and 4) umbilical base excess < -10 mmol/l. Ninety term infants fulfilled the criteria for asphyxia. The parents of 17 infants declined the offer to participate in the study; another 9 infants were not reported to the research team. Therefore, 64 infants were enrolled in the study group. Thirty infants presented with neurological symptoms during the first days after birth (neonatal encephalopathy (NE); Table 1).

Clinical characteristics of the study group are listed in Table 1. Infants with visible congenital anomalies, like malformations, dysmorphic features, chromosomal disorders or heriditary syndromes, were excluded from the

study. The parents of the children gave signed informed consent and the procedures were approved by the Regional Medical Ethical Committee.

Methods

According to the method of General Movements spontaneous motility in supine position of all infants was video recorded twice during the first postnatal months, i.e., at 'writhing' GM age (38 – 47 weeks PMA) and at 'fidgety' GM age (48 – 58 weeks PMA). Care was taken to record at least 5 minutes of spontaneous motility in an awake, active, non-crying state. The GMs were assessed by the first author who was aware of the clinical condition of the infant and by the last author who was blinded to the infant's clinical condition.

Movement quality was classified as normal optimal (NO), normal suboptimal (SO), mildly abnormal (MA) or definitely abnormal (DA), according to Hadders-Algra et al. (2004). NO movements are very variable and complex and fluent. SO movements have a sufficient amount of movement variation and complexity, but are not fluent. MA movements are characterized by a limited amount of variation and complexity, and DA movements by a virtual or total absence of movement variation and complexity.[18] Inter-observer agreement between the two assessors (determined on the basis of a random sample of 60 videos for each age period) was good: writhing period: Cohen's $\kappa = 0.78$, fidgety period: $\kappa = 0.79$. In case of disagreement classification was discussed till consensus was reached.

Data on social class were collected by means of a parental questionnaire. Clinical data and data based on hospital records were collected on standardized forms (table 1). Ultrasound scans of the brain of the asphyxiated infants were made on clinical indication on ages varying from 1 day to 16 days (median: 2 days). In a minority of infants multiple scans had been made. Ultrasound abnormalities were classified according to Daneman et al.[25]

Table 1. Clinical characteristics of the study group

Variables **Prenatal and social characteristics**	Study group n = 64
Male Gender (%)	37(58%)
Maternal education: higher education (%)*	17 (27%)
Presence of complications during pregnancy: - HELLP/ preeclampsia/hypertension - loss of blood/placenta praevia - placental abruption - Rhesus antagonism - imminent preterm labour - hyperglycaemia	21 (33%) 12 (19%) 3 (4%) 3 (4%) 1 (2%) 1 (2%) 1 (2%)
Perinatal characteristics	
Gestational age at birth in weeks: median (range)	40 (36 – 43)
Breech presentation	3 (5%)
Duration first stage in hours: median (range)	8.75 (0 – 24)
Duration second stage in minutes: median (range)	21.5 (0 –240)
Decelerating CTG (%)	41 (64%)
Instrumental delivery	39 (61%)
Neonatal characteristics	
Apgar score after 1 minute: median (range)	3 (0 – 8)
Apgar score after 5 minutes: median (range)	6 (2 – 9)
Birthweight, mean ± SD	3387 ± 630
Small for gestational age, birthweight < P10	7 (11%)
Cord pH, mean ± SD	7.1 ± 0.2
Cord BE, mean ± SD	-15.7 ± 6.5
EEG: - no EEG performed - normal EEG - abnormal EEG **	 30 (47%) 18 (28%) 16 (25%)
Sarnat score †: - no signs of neonatal encephalopathy - Grade I - Grade II - Grade III	 34 (53%) 16 (25%) 13 (20%) 1 (2%)
Clinical seizures	14 (22%)
Neonatal Ultrasound (US) scan of the brain: - no US performed - US normal - US abnormal ‡	 40 (62%) 10 (16%) 14 (22%)
Parenteral feeding > 1 week	8 (13%)
Breastfeeding	49 (77%)
Organfailure : - kidneyfailure - liverfailure - hypoglycaemia ¶ - respiratory problems, no artificial ventilation > 1 organ with failure	 8 (13%) 5 (8%) 8 (13%) 36 (56%) 16 (25%)
Perinatal infection	12 (19%)

* : University education or vocational college,
** : Abnormal EEG findings according to Laroia et al. 1998
† : Score according to Sarnat & Sarnat 1976
‡ : Abnormal US findings according to Daneman et al. 2006
¶ : 1 hour postnatally < 1.6, 3 hours postnatally < 2.7, 24 hours postnatally < 3.0 mmol/liter [Srinivasan 1986]

As it is known that abnormalities in the thalamus and basal ganglia may not be visible on ultrasound during the first week of life,[26-27] we applied the following algorithm for the classification of ultrasound findings: Infants who did not have an ultrasound scan or who had a single assessment with normal findings in the first 6 days of life were classified as having 'missing' ultrasound data. Infants with multiple normal scans or a normal scan after day 6 were classified as having 'normal' scans and the ultrasound finding of those infants who had at least one abnormal ultrasound scan were classified as 'abnormal' (Table 1).

Table 2. Quality of General Movements in the neonatal period ('writhing GM' age) and around 3 months ('fidgety GM' age)

		Quality of GMs at 'fidgety GM' age				
		NO	SO	MA	DA	Total
Quality of GMs at 'writhing GM' age	NO	**0**	1	0	0	1
	SO	2	**7**	5	1	15
	MA	2	15	**7**	2	26
	DA	0	4	12	**6**	22
	Total	4	27	24	9	64

Statistics

Statistics were performed with the software package SPSS, version 12. The analysis focused on the influence of ante-, peri-, and neonatal characteristics on the quality of GMs . Besides univariate statistical analyses with Chi-square, Mann Whitney and t-test, logistic regression analysis was applied to determine which early factors were the major determinants of abnormal GMs in infants with asphyxia. Factors were only entered into the model if the association with GM quality reached a p-value < 0.10. Differences with p-levels < 0.05 were considered statistically significant (two tailed).

Table 3. Relation between early risk factors and definitely abnormal GMs in infants with asphyxia (n=64).

	DA GMs at Writhing age	DA GMs At Fidgety age
Perinatal risk factors		
Duration first stage > 6 hours.	0.08	
Duration second stage > 60 minutes		0.06
Instrumental delivery: vacuum extraction		0.10
Cord pH < 7.20	0.08	
CTG decelerations	0.07	
Presence of at least 2 of the 4 criteria of asphyxia (AS after 5 min. < 7, pH < 7.20; BE < -15; CTG decelerations)	**0.02***	
Neonatal risk factors		
Perinatal infection	0.09	0.06
Sarnat score II or more	**0.01****	**0.02****
Kidneyfailure	**0.0001****	
More than one of following signs of organ failure / clinical sequelae of asphyxia kidney failure; liver failure; hypoglycaemia; respiratory problems with or without the need of artificial ventilation	**0.02***	
Parenteral feeding > 1 week	**0.02****	0.07
Abnormal EEG (n = 34)	**0.05***	
Abnormal US (n = 24)	0.06	**0.02****

Numbers indicate p-values; Statistics preformed: * χ^2 , ** Fisher Exact Test .

Results

Neonatally 22 (34%) infants showed DA GMs and 26 (41%) MA GMs. The quality of GMs had improved at 'fidgety GM' age. At that age 9 (14%) infants had DA GMs and 24 (38%) MA GMs (Table 2). GM-quality of 20 infants (32%) was identical at both ages, it improved in 35 infants (54%) and deteriorated in 9 infants (14%) (Table 2).

Univariate analysis indicated that DA GMs at 'writhing' GM age were related to variables which reflected the degree of organfailure as an immediate clinical consequence of the asphyxia. DA GMs at 'writhing' GM age were related to the presence of at least two of the four criteria of asphyxia, the presence of a Sarnat score > 1, kidney and multiple organ failure, the need of parenteral feeding for at least a week and the presence of abnormalities on EEG (Table 3). DA GMs at 'fidgety' GM age were only related to abnormalities on the neonatal ultrasound scan of the brain and to a Sarnat score > 1 (Table 3).

Multivariate analyses revealed that DA GMs at 'writhing' age were best explained by the presence of at least two of the criteria of asphyxia in combination with failure of at least one organ (Table 4). DA GMs at 'fidgety' GM age were associated in particular with abnormalities on the neonatal ultrasound scan of the brain and a long duration of the second stage of labour (> 1 hour; Table 4).

Table 4. Result of logistic regression analysis of factors contributing to the occurrence of definitely abnormal GM at writhing and fidgety age.

	Odds Ratio (95%CI)	P-value
DA Writhing GMs: explained variance	19.3%	
- Presence of at least 2 of the 4 criteria of asphyxia (pH < 7.20; BE < -10; CTG decelerations; AS 5 min.< 7)	4.44 (1.34, 14.76)	0.02
- More than one of following signs of organ failure / clinical sequelae of asphyxia: kidney failure; liver failure; hypoglycaemia; respiratory problems with or without the need of artificial ventilation	5.80 (1.56, 21.50)	0.009
DA Fidgety GMs: explained variance	17.8%	
- Duration second stage of labour > 60 min.	8.81 (1.44, 53.78)	0.02
- Abnormal ultrasound scan of brain	10.64 (1.75, 64.88)	0.01

Discussion

Our study indicated that in term infants with asphyxia the risk factors for DA GMs in the neonatal period differ from those at the age of 3 months. Early neurological deviancy expressed in the form of DA GMs was associated with acute illness induced by the hypoxic-ischaemic event, whereas neurological morbidity at 3 months was related in particular to neonatal ultrasound scan abnormalities of the brain.

The present study was carried out in a regional hospital. The strengths and weaknesses of the study are related to this specific setting. A weakness of the study was the limited access to neuro-imaging. We only had access to the information on the ultrasound scans of the brain. These ultrasound

scans had been made on indication of the paediatrician and we depended on the radiologist's written report for the details of the findings. The strengths of the study are threefold: 1) evaluation of risk factors for deviant outcome in term infants with asphyxia at birth in a regional hospital, i.e. a non-academic setting, 2) the absence of attrition and 3) the standardized application of a sensitive method to evaluate brain function in young infants.

The asphyxiated infants of the present study showed considerably more often abnormal GMs than term infants in the general population. Less than 4% of the 3-month-old full-term infants in the general population show DA GMs and 25% exhibit mildly abnormal GMs,[28] compared to 14% and 38% of our study group of asphyxiated infants. This finding confirms the increased risk for neurological morbidity after perinatal asphyxia at term.[18,20,29-30] Abnormal GMs at 'writhing' age correlated with perinatal factors associated with asphyxia and its immediate consequences such as organ failure. The study of Bos et al[31] indicated that acute systemic illness such as sepsis may induce abnormal GMs. The present data indicate that in infants with asphyxia DA GMs in the neonatal period were more closely related to the acute illness induced by hypoxia-ischaemia than to lesions of the brain. After the neonatal period this changed. Movement quality of a substantial number of infants with DA GMs at 'writhing' age improved at 'fidgety' age, in general to MA GMs (see Table 2). This means that part of the infants with clinical asphyxia suffered from a transient form of dysfunction only. This finding underscores the young brain's intrinsic potential for recovery. This is one of the major reasons that perinatal adversities only infrequently result in permanent neurological damage ('brain sparing phenomenon').[32] The improvement in the infants with apparently transient dysfunction resulted in the emergence of a clear relationship between abnormalities of the brain detected by means of ultrasound imaging of the newborn brain and DA GMs at 'fidgety' age. The abnormalities on the neonatal ultrasound scans in general consisted of increased signal intensity in the periventricular white matter. This finding fits in with the recently generated hypothesis that abnormal GMs result from

dysfunction or damage of the cortical subplate or its efferent motor connections which run through the periventricular white matter.[28,33]

The data indicated that a duration of the second stage of labour of more than one hour increased the risk for DA GMs at 'fidgety' age. This finding does not correspond to the literature.[34] It still is a matter of dispute whether a prolonged duration of the second stage of labour contributes to adverse neonatal outcome, but a second stage of less than two hours is in general considered as safe.[35-36]

In conclusion, the quality of GMs in the neonatal period is mainly related to acute illness of the asphyxiated infant and not to abnormalities on the ultrasound scan of the brain. This finding reflects the sensitivity of the young brain to react to adverse clinical conditions. Fortunately, part of the early neurological deviancy reflects transient dysfunction only. Due to the disappearance of transient dysfunction, GM-assessment at 3 months, which was related to abnormalities on the neonatal ultrasound scan of the brain, seems to have more clinical importance. As GM-assessment is cheap and non-invasive our findings suggest that this method is a valuable tool to be used to evaluate the integrity of the nervous systems of infants, who suffered from perinatal asphyxia. This may be valid in particular in secondary settings where newly developed imaging techniques are not available. It goes without saying that follow up at school age of the infants studied is highly desirable.

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